(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 October 2006 (12.10.2006)

PCT

(10) International Publication Number
WO 2006/107528 A1

(51) International Patent Classification:
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/US2006/009082

(22) International Filing Date: 13 March 2006 (13.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/093,742 30 March 2005 (30.03.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/107528 A1

(54) Title: NOVEL PHARMACEUTICAL FORMULATION CONTAINING A BIGUANIDE AND A THIAZOLIDINEDIONE DERIVATIVE

(57) Abstract: A pharmaceutical dosage form comprising a controlled release component comprising an antihyperglycemic drug in combination with a second component comprising a thiazolidinedione derivative is herein disclosed and described.

Novel Pharmaceutical Formulation Containing a Biguanide and a Thiazolidinedione Derivative.

This is a continuation-in-part application of United States Patent Application Serial No. 10/777,542 filed on February 12, 2004 which is a continuation-in-part application of United States Patent Application Serial No. 10/664,804 filed on September 19, 2003 and which claims the benefit of United States provisional patent applications Serial Nos. 60/412,180 and 60/412,181 filed on September 20, 2002.

BACKGROUND OF THE INVENTION

The present invention relates to a pharmaceutical dosage form comprising an antihyperglycemic drug, in combination with a thiazolidinedione derivative. More specifically, the present invention relates to an oral dosage form comprising a biguanide e.g. metformin or buformin or a pharmaceutically acceptable salt thereof e.g., metformin hydrochloride or the metformin salts described in U.S. Pat. Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference in combination with a thiazolidinedione derivative as described in U.S. Pat. No. 4,687,777 also incorporated herein by reference.

Many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

For example, extended release tablets have been described which have an osmotically active drug core surrounded by a semipermeable membrane. These tablets function by allowing the aqueous component of a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so the resultant drug solution can be released through a passageway in the coating membrane. Alternatively, if the active ingredient is insoluble in the permeating fluid, it can be pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,034,758; 4,077,407 and 4,783,337. U.S. Pat. No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable membrane only after sufficient pressure has

developed within the membrane to burst or rupture the membrane at a weak portion of the membrane.

The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example, U.S. Pat. Nos. 4,777,049 and 4,851,229 describe osmotic dosage forms comprising a semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane, e.g. U.S. Pat. Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core, e.g. U.S. Pat. Nos. 5,650,170 and 4,892,739.

Certain controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride have been limited to the use of an expanding or gelling agent to control the release of the drug from the dosage form. This limited research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE™ XR product insert which is a controlled release metformin HCl product commercially available from Bristol-Myers Squibb Co.

Thiazolidinedione derivatives have been described in U.S. Pat. No. 4,687,777. The therapeutic value of these compounds in combination therapy has further been described in U.S. Pat. Nos. 5,859,037; 5,952,356; 5,965,584; 6,150,384 and 6,172,090. However, none of these patents describe a dosage form having the advantages of the subject invention.

Pharmaceutical dosage forms containing combinations of antihyperglycemic drugs and thiazolidinedione derivatives have been proposed in the art. For example, EPO 0 749 751 (which is incorporated herein by reference) teaches pharmaceutical compositions comprising an insulin sensitivity enhancer, which could be a thiazolidinedione compound, in combination with other antidiabetics. More specifically, EPO 0 749 751 teaches that the preferred insulin sensitivity enhancer is pioglitazone, which can be combined with other antidiabetics such as metformin, phenformin or buformin, and further that these drugs can be associated (mixed and/or coated) with conventional excipients to provide taste masking or sustained release behavior. Another example of a combination of antihyperglycemic drugs and

thiazolidinedione derivatives is U.S. Pat. No. 6,011,049, (which is incorporated herein by reference). This patent teaches a single pharmaceutical composition that contains pioglitazone or trolitazone and metformin in slow release forms such as osmotic pumps or skin patches. Other combinations of antihyperglycemic drugs and thiazolidinedione derivatives can be found in U.S. Pat. Nos. 6,524,621; 6,475,521; 6,451,342 and 6,153,632 and PCT patent applications WO 01/3594 and WO 01/ 3594, which are incorporated herein by reference.

Also known in the art are WO 99/47125 and United States Patent No. 6,099,862 that disclose a metformin osmotic tablet coated with an immediate release coating containing an antihyperglycemic or a hypoglycemic drug.

Although the prior art teaches pharmaceutical dosage formulations that contain both an antihyperglycemic compound and thiazolidinedione derivatives, the present invention provides numerous benefits over the prior art teachings as will be described below.

It is an object of the present invention to provide a dosage form comprising a first active drug, which is formulated to provide a controlled or sustained release delivery. Preferably, the first active drug is an antihyperglycemic compound. The present invention further provides for a second active drug which preferably is a thiazolidinedione derivative. The novel dosage form described herein provides for delivery of first and second active drugs such that the bioavailability of either drug is not decreased by the presence of food.

It is a further object of the present invention to provide a dosage form, as described above, comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound, wherein said controlled or sustained release mechanism is not regulated by an expanding polymer, in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative.

It is also a further object of the present invention to provide a dosage form as described above, comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative that can provide continuous and non-pulsating therapeutic levels of said antihyperglycemic drug to an animal or human in need of such treatment over a eight hour to twenty-four hour period.

It is an additional object of the present invention to provide a dosage form comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative that obtains peak plasma levels of the antihyperglycemic compound approximately 6-12 hours after administration following a meal and peak plasma levels of thiazolidinedione derivative approximately 1-4 hours after dosing.

It is also an object of the present invention to provide a dosage form comprising a first active drug as a controlled or sustained release pharmaceutical core tablet having only a homogeneous osmotic core wherein the osmotic core component may be made using ordinary tablet compression techniques.

It is an additional object of the present invention to provide a dosage form comprising delivery of a first active drug as a controlled or sustained release formulation for an antihyperglycemic compound in combination with delivery of a second active drug by immediate release comprising a thiazolidinedione derivative that obtains peak plasma levels of the antihyperglycemic compound approximately 6-12 hours after administration and peak plasma levels of thiazolidinedione derivative approximately 1-4 hours after dosing when the product is dosed following a meal.

It is a further object of the present invention to provide a dosage form comprising an antihyperglycemic drug as a controlled or sustained release component and a thiazolidinedione derivative as an immediate release component, wherein not less than 80% of the total amount of the thiazolidinedione derivative is released from the dosage form within 30 minutes or less.

It is a further additional object of the present invention to provide a shelf stable dosage form comprising an antihyperglycemic drug as a controlled or sustained release component and a thiazolidinedione derivative as an immediate release component, wherein the total amount of thiazolidinedione related compounds or impurities are not more than 0.6% after two years of storage and no individual related compound or impurity is more than 0.2 %.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical dosage form comprising a first active drug, preferably an antihyperglycemic drug, in combination with a second active drug, preferably a thiazolidinedione derivative. More specifically, the present

invention relates to an oral dosage form comprising a first active drug comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof e.g., metformin hydrochloride or the metformin salts, in combination with a second active drug comprising a thiazolidinedione derivative.

The foregoing objectives are met by a dosage form comprising a first and second active drug, wherein the first active drug is formulated as a controlled release core, preferably an osmotic tablet, with or without a gelling or expanding polymer. The second active ingredient may be part of the controlled release core or it may preferably be combined with the controlled release core in a manner that provides for immediate release of the second active ingredient. For example, the second active ingredient can be incorporated into a membrane that is applied to the core or the second active ingredient may be applied to a coated or uncoated controlled release core.

In one embodiment the second active drug, which may be the thiazolidinedione derivative, is provided as an immediate release formulation in the dosage form whereas the antihyperglycemic component is provided as a controlled release formulation in the dosage form. This immediate release portion of the formulation should provide peak plasma levels (T_{max}) of 1-12 hours preferably, 1-4 hours of the thiazolidinedione derivative, while the controlled release portion of the formulation may provide peak plasma levels (T_{max}) of 6-12 hours of the antihyperglycemic component when dosed following a meal.

Preferably, the dosage form according to the subject invention may be administered once a day, preferably with or after a meal, and most preferably with or after the evening meal. The subject dosage form can provide therapeutic levels of the drug throughout the day with peak plasma levels (T_{max}) of the antihyperglycemic drug being obtained between 6-12 hours after administration with a meal.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention concerns a pharmaceutical formulation or dosage form comprising a first active drug comprising an antihyperglycemic drug in combination with a second active drug comprising a thiazolidinedione derivative. Preferably, the antihyperglycemic drug is a biguanide e.g. metformin or buformin or a pharmaceutically acceptable salt thereof. The antihyperglycemic drug is delivered in a controlled release manner from a tablet core, preferably an osmotic tablet core with

or without a gelling or swelling polymer. The tablet core should include the antihyperglycemic drug and at least one pharmaceutically acceptable excipient. In one embodiment of the present invention the tablet core includes the antihyperglycemic drug, a binding agent and an absorption enhancer, and the tablet core is preferably coated with a polymeric coating to form a membrane around the tablet and drilled to create one passageway on each side of the membrane. The second active drug comprises a thiazolidinedione derivative, and is preferably applied to the membrane of the tablet core and provides for either immediate or controlled release of said thiazolidinedione derivative.

The term, antihyperglycemic drugs as used in this specification, refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Antihyperglycemic drugs include the biguanides such as metformin, phenformin or buformin or the like, and pharmaceutically acceptable salts, isomers or derivatives thereof.

The term thiazolidinedione derivative as used in this specification refers to drugs that are useful for controlling or managing NIDDM. These include, but are not limited to, troglitazone, rosiglitazone, pioglitazone, ciglitazone or the like, and pharmaceutically acceptable salts, isomers or derivatives thereof.

The term binding agent refers to any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, polymethacrylate, polyvinylalcohol and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble materials such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent may comprise approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core. In one embodiment, the use of a binding agent in the core is optional.

In a preferred embodiment, the core may optionally comprise an absorption enhancer. The absorption enhancer can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant (anionic, cationic, amphoteric), a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are lecithin, fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants such as sodium lauryl sulfate, sodium taurocholate and

polysorbate 80, chelating agents such as citric acid, phytic acid, ethylenediamine tetraacetic acid (EDTA) and ethylene glycol-bis(β-aminoethyl ether)-N,N,N,N-tetraacetic acid (EGTA). The core may comprise approximately 0 to about 20% of the absorption enhancer based on the total weight of the core and most preferably about 2% to about 10% of the total weight of the core.

In one embodiment of the present invention, which does not employ a gelling or swelling polymer, the core of the present invention is preferably formed by granulating an antihyperglycemic drug with a binding agent and compressing the granules with the addition of a lubricant and absorption enhancer into a tablet. The core may also be formed by dry granulating the core ingredients by passing them through a roller compactor and compressing the granules with the addition of a lubricant into tablets. Direct compression may also be employed for tabletting. Other commonly known granulation procedures are known in the art. Additionally, other excipients such as lubricants, pigments or dyes may also be employed in the formulation of the subject invention.

The term gelling or swelling polymer refers to polymers that gel, swell or expand in the presence of water or biological fluids. Representative examples of gelling or swelling polymers are high molecular weight hydroxpropyl methylcellulose (such as METHOCEL® K100M, which is commercially available from Dow Chemical) and high molecular weight polyethylene oxides (such as POLYOX WSR 301, WSR 303 or WSR COAGULANT). Other gelling or swelling polymers are described in United States Patent No. 4,522,625 (which is incorporated herein by reference).

The core formed as described herein, can be coated with a membrane or sustained release coating. Materials that are useful in forming the membrane or sustained release coating are ethylcellulose, cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate propionate and cellulose acetate butyrate. Other suitable polymers are described in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,008,719; 4,036,228 and 4,612,008 (which are incorporated herein by reference). The most preferred membrane or sustained release coating material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, and is commercially available from Eastman Fine Chemicals.

In an alternative embodiment, the membrane or sustained release coating can include one of the above-described polymers and a flux-enhancing agent. The flux enhancing agent can increase the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through the passageway and/or the porous membrane. The flux-enhancing agent can be a water-soluble material or an enteric material. Examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycols (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers, poloxamers (such as LUTROL F68, LUTROL F127, LUTROL F108 which are commercially available from BASF) and mixtures thereof. A preferred flux-enhancer is PEG 400.

The flux enhancer may also be a drug that is water soluble such as metformin or its pharmaceutically acceptable salts, or the flux enhancer may be a drug that is soluble under intestinal conditions. If the flux enhancer is a drug, the present dosage form has the added advantage of providing an immediate release of the drug that has been selected as the flux enhancer.

The flux enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the membrane or sustained release coating to form channels in the membrane or sustained release coating which enables fluid to enter the core and dissolve the active ingredient.

The membrane or sustained release coating may also be formed using a commonly known excipient such as a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, polyethylene glycols (PEG) (i.e PEG 400, PEG 8000), acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate and the like. Depending on the particular plasticizer, amounts from about 0 to about 25%, and

preferably about 2% to about 15% of the plasticizer can be used based upon the total weight of the membrane or sustained release coating.

Generally, the membrane or sustained release coating around the core will comprise from about 1% to about 10% and preferably about 2% to about 5% based upon the total weight of the core and coating.

In a preferred embodiment, the membrane or sustained release coating surrounding the core further comprises a passageway that will allow for controlled release of the drug from the core. As used herein the term passageway includes an aperture, orifice, bore, hole, weakened area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form. Passageways used in accordance with the subject invention are well known and are described in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,034,758; 4,077,407; 4,783,337 and 5,071,607.

Independent of the antihyperglycemic is a second active drug, preferably a thiazolidinedione derivative. This second active drug may be formulated to provide an immediate release of the thiazolidinedione derivative. In one embodiment of the present invention the thiazolidinedione derivative is applied in the form of a layer to a controlled or sustained released core comprising the antihyperglycemic drug. The thiazolidinedone derivative layer employs a binder and other conventional pharmaceutical excipients such as absorption enhancers, surfactants, plasticizers, antifoaming agents and combinations of the foregoing. An absorption enhancer may be present in the thiazolidinedione derivative layer in an amount up to about 30% w/w in comparison to the weight of the thiazolidinedione derivative. A binding agent may be present in an amount up to 150% w/w of the thiazolidinedione derivative.

In one embodiment the binder in the thiazolidinedone derivative layer is a water soluble binder, preferably a water soluble film forming binder, which has a low viscosity, typically less than 50 mPa.S, preferably less than 25 mPa.S, and most preferably less than 10 mPa.S, when tested as a 2% aqueous solution at 20°C. An example of such a water soluble binder is hydroxypropyl cellulose available from Nippon Soda Co., Ltd of Japan under the tradename HPC-SSL and HPC-SL which have a reported viscosity of 2-3 mPa.S and 3-6 mPa.S respectively.

If a surfactant is employed in the thiazolidinedone derivative layer it is preferred that the surfactant be a non-ionic surfactant such a polaxamer.

A second active drug immediate release formulation may be incorporated into a single dosage form by coating onto the membrane or sustained release coating of the dosage form by conventional methods. Alternatively, it may be incorporated by any pharmaceutically acceptable method into a single dosage form with the first active drug. The incorporation of the second active drug may be performed by, but would not be limited to, the processes selected from the group consisting of drug layering, lamination, dry compression, deposition and printing.

When the thiazolidinedione derivative is coated onto a membrane or sustained release coating of an osmotic tablet core, the thiazolidinedione coating should be applied from a coating solution or suspension that employs an aqueous solvent, an organic solvent or a mixture of an aqueous and an organic solvent. Typical organic solvents include acetone, isopropyl alcohol, methanol and ethanol. If a mixture of aqueous and organic solvents is employed, the ratio of water to organic solvent should range from 98:2 to 2:98, preferably 50:50 to 2:98, most preferably 30:70 to 20:80 and ideally about 25:75 to 20:80. If a mixed solvent system is employed, the amount of binder required for coating the thiazolidinedione derivative onto the membrane or sustained release coating may be reduced. For example, successful coatings have been obtained from a mixed solvent system where the ratio of binder to thiazolidinedione derivative is 1:9 to 1:11. Although acceptable coatings can be obtained when the thiazolidinedione coat is applied directly to the membrane or sustained release coating, a preferred approach is to first coat the membrane or sustained release coating with a seal coat prior to the application of the thiazolidinedione coating. As used herein a seal coat is a coating that does not contain an active pharmaceutical ingredient and that rapidly disperses or dissolves in water. It may be necessary to apply about 5 to 20% excess, preferably about 10-15% excess of the thiazolidinedione coating solution to account for losses during the coating process.

The thiazolidinedione coating solution or suspension may also contain a surfactant and a pore forming agent. A pore forming is preferably a water-soluble material such as sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycols (PEG), and propylene glycol. In an alternative embodiment, the dosage form of the present invention may also comprise an effective immediate release amount of the antihyperglycemic drug. The effective immediate release amount of antihyperglycemic drug may be coated onto the membrane or sustained

release coating of the dosage form or it may be incorporated into the membrane or sustained release coating.

In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants, etc., which are disclosed in Remington's Pharmaceutical Sciences (1995), may be used to optimize the above listed formulations of the subject invention.

Biguanides, such as metformin are commonly administered in dosage forms containing 500 mg, 750 mg, 850 mg, and 1000 mg. Thiazolidinedione derivatives, for example pioglitizone, are commonly administered in dosage forms containing 15 mg, 30 mg and 45 mg. The present invention is intended to encompass the above listed therapeutic combinations, without providing a specific example of each possible combination of compounds and their respective dosage amounts.

A preferred embodiment the dosage form will have the following composition:

FIRST ACTIVE DRUG		
Core:	Amount (% of core)	
drug	50-98%	(75-95% preferred)
binder	0.1-40%	(3-15% preferred)
absorption enhancer	0-20%	(2-10% preferred)
lubricant	0-5%	(0.5-1% preferred)
Coating:	Amount (% of coating)	
polymer	50-99%	(75-95% preferred)
flux enhancer	0-40%	(2-20% preferred)
plasticizer	0-25%	(2-15% preferred)

SECOND ACTIVE DRUG	Amount (% of total dosage form)	
drug	0.1-20%	(1-10% preferred)
binder	0.1-30%	(1-20% preferred)
surfactant	0 - 20%	(0.1-15% preferred)
pore former	0 - 25%	(0.1-15% preferred)
plasticizer	0 - 20%	(0.1-15% preferred)

The dosage forms prepared according to the present invention exhibit the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C.:

Release of First Active Drug

Time (hours)	% release	
2	0-25%	(0-20% preferred)
4	10-45%	(20-40% preferred)
8	30-90%	(45-90% preferred)
12	NLT 50%	(NLT 60% preferred)
16	NLT 60%	(NLT 70% preferred)
20	NLT 70%	(NLT 80% preferred)

NLT = NOT LESS THAN

Release of Second Active Drug

Time (hours)	% release	
0.5	NLT 60%	(NLT 75% preferred)

It has been discovered that the selection of the excipients for use in the thiazolidinedione component of the dosage form can greatly affect the release characteristics, potency and stability of the thiazolidinedione. Therefore, in an alternate embodiment of the present invention, the composition of the thiazolidinedione component of the present invention should be selected so that not less than 85%, preferably not less than 90% and most preferably not less than 95% of the thiazolidinedione is released from the dosage form within 45 minutes, preferably within 40 minutes and most preferably within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

Further the excipients for use in the thiazolidinedione component of the dosage form should be selected so that the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6%, preferably not more than 0.5% and most preferably not more than 0.25% and each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%, preferably not more than 0.2% and most preferably not more than 0.1%. The thiazolidinedione related compounds or impurities in the final dosage form are

determined by High Performance Liquid Chromatography (HPLC) using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm or equivalent column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, about a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV detector.

EXAMPLES

The following are provided by way of example only and are in no means intended to be limiting.

EXAMPLE 1

A controlled release tablet containing 850 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

First Active Drug

I. Core	(% composition of core)
Metformin HCl	90.54%
Povidone K-30[1], USP	4.38%
Sodium Tribasic Phosphate	4.58%
Magnesium stearate	0.5%

[1] approximate molecular weight = 50,000; dynamic viscosity (10% w/v solution at 20°C) = 5.5-8.5 mPa·s.

(a) Granulation

The metformin HCl is delumped by passing it through a 40 mesh screen and collecting it in a clean, polyethylene-lined container. The povidone, K-30, and sodium tribasic phosphate are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying the binding solution of povidone and sodium tribasic phosphate under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

As stated above, the orifice may be formed by any means commonly employed in the pharmaceutical industry.

(c) Seal Coating (optional)

The core tablet can be seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear, in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C.; atomization pressure of 28-40 psi and spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2-4% is obtained.

II Membrane	(% composition of membrane)
Cellulose Acetate (398-10)[2]	85%
Triacetin	5%
PEG 400	10%

[2] acetyl content 39.3-40.3%

(a) Membrane Coating Process

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The clear membrane coating solution is then sprayed onto the seal coated tablets using a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars and spray rate of 120-150 ml/min. The

sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

III. Second Active Drug Layering	(% composition of second component)
Pioglitizone HCl	43.5%
Tween 80	2.0%
Hydroxypropyl methylcellulose	54.5%

Tween 80 and hydroxypropyl methylcellulose are dissolved in purified water. Pioglitizone HCl is then dispersed into this solution. The resulting suspension is then sprayed onto the above-membrane-coated tablets.

EXAMPLE 2

A controlled release tablet containing 850 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

First Active Drug

I. Core	(% composition of core)
Metformin HCl	88.555%
Povidone K-90[3], USP	6.368%
Sodium Lauryl Sulfate	4.577%
Magnesium Stearate	0.5%

[3] approximate molecular weight = 1,000,000, dynamic viscosity (10% w/v solution) 300-700 mPa·s at 20°C.

(a) Granulation

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90, is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

As stated above, the orifice may be formed by any means commonly employed in the pharmaceutical industry.

(c) Seal Coating (optional)

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi and spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II

Membrane	(% composition of membrane)
Cellulose Acetate (398-10)[4]	85%
Triacetin	5%
PEG 400	10%

[4] acetyl content 39.3-40.3%

(a) Membrane Coating Process

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred. The coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product

temperature of 16-22°C; atomization pressure of approximately 3 bars and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

III.	Second Active Drug Layering	(% composition of second component)
	Pioglitizone HCl	43.5%
	Tween 80	2.0%
	Hydroxypropyl methylcellulose	54.5%

Tween 80 and hydroxypropyl methylcellulose are dissolved in purified water. Pioglitizone HCl is then dispersed into this solution. The resulting suspension is then sprayed onto the above described tablets.

EXAMPLE 3

A controlled release tablet containing 500 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

I. First Active Drug

A 500 mg metformin membrane coated tablet is prepared as described in Example 2 above except that compound cup toolings are used during tableting. The 500 mg metformin membrane coated tablet has the following composition:

CORE	
Metformin HCl	500 mg/tablet
Povidone K-90, USP	35.96 mg/tablet
Sodium lauryl sulfate, NF	25.84 mg/tablet
Magnesium stearate, NF	2.82 mg/tablet
SEAL COATING	
Opadry Clear (YS-1-7006)	23.53 mg/tablet
MEMBRANE COATING	
Cellulose Aacetate, 398-10, NF	23.56 mg/tablet
Triacetin, USP	1.39 mg/tablet
Polyethylene Glycol 400, NF	2.77 mg/tablet
Total weight	615.87 mg/tablet

II. Second Active Drug Layering

An immediate release amount of pioglitiazone HCL is applied to the 500 mg metformin HCl membrane coated tablet prepared in step I. The final tablet has the following composition:

Metformin HCl membrane coated	615.87 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	16.53 mg/tablet
Tween 80	2.0 mg/tablet
Polyplasdone XL	15.0 mg/tablet
Opadry Clear (YS-1-7006)	8.47 mg/tablet
Color Coating	
Opadry White	10.0 mg/tablet
Polishing Coat	
Candelilla Wax Powder	2.0 mg/tablet

The pioglitazone coating is directly applied to the 500 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by dissolving 0.252 kg of Opadry Clear, 0.269 kg of Polyplasdone XL and 0.036 kg of Tween 80 in 9.908 kg of purified water using a homogenizer. Once these ingredients are dissolved, 0.296 kg of pioglitazone HCl is dispersed into the solution and homogenized. The homogenized dispersion is then directly applied to the 500 mg metformin HCl membrane coated tablets using a 24"O'Hara Labcoat III pan coater with the following conditions:

Spray Rate	15-27 mL/min
Exhaust Temperature	42-47°C
Atomization Air Pressure	25 psi
Pan Speed	5-9 rpm
Inlet Air Flow	300-400 CFM

Once the pioglitazone coating has been applied to the 500 mg metformin HCl membrane coated tablet, an aesthetic or color coating of Opadry white is applied to the pioglitazone coated tablet. The color coating is prepared by dispersing 0.179 kg of Opadry White in 1.791 kg of purified water. The Opadry White suspension is

applied to the pioglitazone coated tablet using a 24" O'Hara Labcoat III pan coater under the following conditions:

Spray Rate	20-35 mL/min
Exhaust Temperature	35-45°C
Atomization Air Pressure	25 psi
Pan Speed	9 rpm
Inlet Air Flow	390-500 CFM

Once the color coating is applied, the tablets are polished using 0.036 kg of Candelilla wax powder.

EXAMPLE 4

A controlled release tablet containing 500 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

I. First Active Drug

A 500 mg membrane coated tablet is prepared as described in Example 2 above except that compound cup toolings are used during tableting. The 500 mg membrane coated tablet has the following composition:

CORE	
Metformin HCl	500 mg/tablet
Povidone K-90, USP	35.96 mg/tablet
Sodium Lauryl Sulfate, NF	25.84 mg/tablet
Magnesium Stearate, NF	2.82 mg/tablet
SEAL COATING	
Opadry Clear (YS-1-7006)	23.53 mg/tablet
MEMBRANE COATING	
Cellulose Acetate, 398-10, NF	23.56 mg/tablet
Triacetin, USP	1.39 mg/tablet
Polyethylene Glycol 400, NF	2.77 mg/tablet
Total weight	615.87 mg/tablet

II. Second Active Drug Layering

An immediate release amount of pioglitiazone HCL is applied to the 500 mg metformin HCl seal coated tablet prepared in Step I. The final tablet has the following composition:

Metformin HCl membrane coated tablet	615.87 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	13.8 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	16.53 mg/tablet
Tween 80	2.0 mg/tablet
Sodium Chloride	4.27 mg/tablet
Opadry Clear (YS-1-7006)	2.0 mg/tablet
Color Coating	
Opadry White	8.10 mg/tablet
Polishing Coat	
Candelilla Wax	0.20 mg/tablet

The seal coating solution is prepared by dissolving 0.258 kg of Opadry Clear in 2.576 kg of purified water and spraying the solution onto approximately 12.088 kg of the 500 mg membrane coated metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater. The seal coat is applied under the following conditions:

Spray Rate	20-35 mL/min
Exhaust Temperature	35-45°C
Atomization Air Pressure	25 psi
Pan Speed	9 rpm
Inlet Air Flow	390-500 CFM

The pioglitazone coating is applied to the seal coated 500 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by dissolving 0.040 kg of Opadry Clear, 0.085 kg of sodium chloride and 0.040 kg of Tween 80 in 4.915 kg of purified water using a homogenizer. Once these ingredients are dissolved, 0.328 kg of pioglitazone HCl is dispersed into the solution and homogenized. The homogenized dispersion is then applied to the seal coated 500 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater with the following conditions:

Spray Rate	10-30 mL/gun/min
Exhaust Temperature	35-45°C
Atomization Air Pressure	20-40 psi
Pattern Air Pressure	20-40 psi
Pan Speed	8-12 rpm
Inlet Air Flow	250-450 CFM.

Once the pioglitazone coating has been applied to the seal coated 500 mg metformin HCl membrane coated tablets, an aesthetic or color coating of Opadry White is applied to the pioglitazone coated tablet. The color coating is prepared by dispersing 0.159 kg of Opadry White in 1.585 kg of purified water. The Opadry White suspension is applied to the pioglitazone coated tablet using conditions similar to those described above for application of the seal coating. Once the color coating is applied, the tablets are polished using 0.004 kg of Candelilla wax powder.

EXAMPLE 5

A controlled release tablet containing 1000 mg of metformin HCl and 30 mg pioglitazone is prepared as follows:

I. First Active Drug

A. Core	(% composition of core)
Metformin HCl	88.07%
Povidone K-90[3], USP	6.87%
Sodium Lauryl Sulfate	4.55%
Magnesium Stearate	0.5%

[3] approximate molecular weight = 1,000,000, dynamic viscosity (10% w/v solution) 300-700 mPa·s at 20°C.

Approximately 206.34 kg of purified water is added to a stainless steel tank followed by approximately 10.86 kg of povidone K-90. The solution is mixed at about 330-360 rpms for about 45 minutes or until the povidone is completely dissolved. Approximately 139.14 kg of metformin HCl is passed through a Comil equipped with a #813 screen and no spacer at 840-850 rpms.

The screened metformin HCl is loaded into a GPCG-60 (Glatt) brand fluidized bed coater with Wurster insert (size 32" by 35 mm high) with 3 nozzles of size 1.5 mm. The metformin HCl is fluidized and the product temperature is adjusted to about 38-43°C. The povidone solution is sprayed onto the fluidized metformin HCl with an atomization pressure of about 2.5-3.0 bars and the pump rate of:

0-15 minutes	491-515 g/min (target 500g/min)
16-30 minutes	680-710 g/min (target 700 g/min)
31-45 minutes	860-910 g/min (target 900 g/min)
46-60 minutes	1090-1170 g/min (target 1100 g/min)
61 minutes to end	1170-1220 g/min (target 1200 g/min).

Once the povidone solution has been consumed, the granules are dried in the fluidized bed at about 2100 CFM and 60°C inlet air temperature until the loss on drying (LOD) is not more than 2%. The resulting granules are passed through a Comil equipped with a #1143 stainless steel screen and a #075 spacer at a speed of 1086-1088 rpms to produce approximately 150 kg of metformin HCl granules. The granulation process is repeated a second time to produce appromixately 300 kg of metformin HCl granules.

Approximately 300 kg of the metformin granules are added to a 50 cu. Ft. Slant-Cone blender along with approximately 14.38 kg of sodium lauryl sulfate and blended for about 20 minutes. About 1.58 kg of magnesium stearate is passed through a #40 mesh stainless steel screen then added to the mixture in the Slant-Cone blender. The resulting mixture is blended for about 5 minutes then compressed into tablets using a conventional tablet press equipped with a ½" round compound cup die, a pre-compression force of 6 and a main compression force of 38. The resulting tablets exhibit a weight range of 1044 g to about 1226 g with a target weight of 1135g, hardness of 20-36 kp (target of 28 kp) and a friability of less than or equal to 0.8%

B. Seal Coating

About 57.61 kg of the core tablets prepared above are seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably about 3.98 kg of Opadry Clear YS-1-7006) in about

21.49 kg of purified water. The Opadry solution is then sprayed onto the core tablet using an O'Hara Lab Coat III pan coater with a 36" pan, 3 spray guns under the following conditions: exhaust air temperature of 40-47°C; atomization pressure of 50± 10 psi, and spay rate of 180±60 g/min/3 guns, pan speed of 4-8 rpms and air volume of 1000±200 CFM. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2.8-4.4% is obtained.

C. Membrane Coating

A cellulose acetate membrane coating is applied to the seal coated metformin HCl tablet cores to produce membrane coated metformin HCl tablets with the following composition:

Metformin HCl 1000mg Tablet	98.456%
Cellulose Acetate (398-10)[4]	1.313%
Triacetin	0.077%
PEG 400	1.54%

[4] acetyl content 39.3-40.3%

Approximately 29.95 kg of acetone is added to a stainless steel tank followed by about 0.788 kg of cellulose acetate and mixed for about 20 minutes until the solution becomes clear. Once the solution is clear about 0.092 kg of polyethylene glycol 400 is added to the solution and mixed for about 5 minutes followed by the addition of about 0.046 kg of triacetin. The solution is mixed for an additional 5 minutes.

About 59.07 kg of the seal coated metformin HCl tablets are loaded into a GPCG-60 (Glatt) brand fluidized bed coater with Wurster insert (size 18" by 45 mm high) with a nozzle of size 1.5 mm. The seal coated metformin HCl tablets areis fluidized and the product temperature is adjusted to about 21±3°C. The cellulose acetate solution is sprayed onto the fluidized seal coated metformin HCl tablets with an atomization pressure of about 2.0-3.0 bars, air volume of 1600 ± 300 CFM and a spray rate of 400±100 g/min until a weight gain of 1-2% (target 1.38%) is obtained. Once the desired amount of membrane coating has been applied the membrane coated

tablets are dried in the fluidized bed 21±3°C and 1350±100 CFM for about 10 minutes followed by 40°C and 1350±100 CFM for about 5 minutes.

The resulting membrane coated tablets are laser drilled to create an orifice in the approximate center of each side of the membrane coated tablet (i.e 2 orifices) with an average diameter of 0.5 mm per orifice. The top micrometer is 6.5 ± 2 mm, bottom micrometer is 6.75 ±2 mm, the pulse width of the laser is 170±70 and pulse delay of 340 ±150 and 350 ±150 respectively.

II. Second Active Drug

An immediate release amount of pioglitazone HCL is applied to the 1000 mg metformin HCl membrane coated tablets prepared in step I. The final tablet has the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coating	
Opadry Clear (YS-1-7006)	16.0 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Sodium Chloride	4.27 mg/tablet
Opadry Clear (YS-1-7006)	3.0 mg/tablet
Color Coating	
Opadry II White (Y-22-7719)	20.27 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

The seal coating is prepared by dispersing 0.174 kg of Opadry Clear in 3.478 kg of ethanol and mixing the dispersion for 15 minutes. The dispersion is than sprayed onto approximately 13.174 kg of the 1000 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater. The seal coat is applied to the 1000 mg metformin HCl membrane coated tablets with the following conditions:

Spray Rate	10-30 ml/gun/min
Exhaust Temperature	25-45°C
Atomization Air Pressure	20-40 psi
Pan Speed	6-12 rpms
Pattern Air Pressure	20-40 psi

Inlet Air Flow	250-450 CFM

The pioglitazone coating then is applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by dissolving 0.036 kg of Opadry Clear and 0.046 kg of sodium chloride in 5.344 kg of ethanol using a homogenizer. Once the ingredients are dispersed, 0.359 kg of pioglitazone HCl is dispersed into the solution and homogenized. The homogenized dispersion is then applied to the seal coated 1000 mg metformin HCl membrane coated tablets using a 24" O'Hara Labcoat III pan coater with the following conditions:

Spray Rate	10-30 mL/gun/min
Exhaust Temperature	25-45°C
Atomization Air Pressure	20-40 psi
Pan Speed	6-12 rpm
Pattern Air Pressure	20-40 psi
Inlet Air Flow	250-450 CFM

Once the pioglitazone coating has been applied, an aesthetic or color coating of Opadry II White is applied to the pioglitazone coated tablets. The color coating is prepared by dispersing 0.220 kg of Opadry II White in 4.407 kg of ethanol. The Opadry II White suspension is than applied to the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater using conditions similar to those described above for the seal coating. Once the color coating is applied, the tablets are polished using 0.004 kg of Candelilla wax powder.

EXAMPLE 6

A controlled release tablet containing 1000 mg of metformin HCl and 30 mg pioglitazone is prepared as follows:

I. First Active Drug

A 1000 mg membrane coated tablet is prepared as described in Example 5 above. The 1000 mg membrane coated tablet has the following composition:

CORE

Metformin HCl	1000 mg/tablet
Povidone K-90, USP	78.0 mg/tablet
Sodium Lauryl Sulfate, NF	51.69 mg/tablet
Magnesium Stearate, NF	5.65 mg/tablet

SEAL COATING

Opadry Clear (YS-1-7006)	47.05 mg/tablet
MEMBRANE COATING	
Cellulose Acetate, 398-10, NF	15.77 mg/tablet
Triacetin, USP	0.92 mg/tablet
Polyethylene Glycol 400, NF	1.85 mg/tablet
Total weight	1201.0 mg/tablet

II. Second Active Drug

An immediate release amount of pioglitazone HCL is applied to the 1000 mg metformin HCl membrane coated tablets prepared in step I. The final tablet has the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	21.0 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Sodium Chloride	5.0 mg/tablet
Opadry Clear (YS-1-7006)	3.7 mg/tablet
Color Coating	
Opadry II White (Y-22-7719)	21.54 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

The seal coat is applied to the 1000 mg metformin HCl membrane coated tablet. The seal coating is prepared by dispersing 0.229 kg of Opadry Clear in 4.573 kg of alcohol USP and mixing the dispersion for 15 minutes. The dispersion is then sprayed onto approximately 13.08 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25°C ± 5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	200±100 CFM

Pattern Air Pressure	10-40 psi

The seal coating dispersion is continuously stirred until it is consumed during the coating process.

The pioglitazone coating then is applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating is prepared by mixing 4.434 kg of alcohol USP and 1.250 kg of purified water (approximately a 78:22 alcohol to purified water ratio) and slowly dispersing 0.040 kg of Opadry Clear into the solvent mixture. Once the Opadry Clear is dispersed, it is homogenized for about 10 minutes. Once the Opadry Clear dispersion is homogenized, 0.054 kg of sodium chloride is added to the dispersion and homogenized for about 2 minutes. After the sodium chloride is homogenized, 0.360 kg of pioglitazone HCl is slowly dispersed into the solvent mix and then homogenized for about 10 minutes. Once the pioglitazone HCl is homogenized, the homogenizer is removed from the mixing vessel and replaced with an air mixer and mixed for an additional 15 minutes. The pioglitazone suspension is stirred until the suspension is consumed during the coating process. The pioglitazone HCl suspension is applied to the seal coated 1000 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed with the following conditions:

Spray Rate	25±10 mL/gun/min
Exhaust Temperature	25±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms
Pattern Air Pressure	10-40 psi
Supply Air Flow	200±100 CFM

Once the pioglitazone coating has been applied to the seal coated 1000 mg metformin HCl membrane coated tablets, an aesthetic coating of Opadry II White is applied to the pioglitazone coated tablet. The aesthetic coating is prepared by dispersing 0.235 kg of Opadry II White (Y-22-7719) in 4.691 kg of alcohol USP and mixing the dispersion for about 1 hour. The Opadry II White dispersion is than sprayed onto the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25°C±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	200±100 CFM
Pattern Air Pressure	10-40 psi

The color coating dispersion is continuously stirred until the dispersion is consumed during the coating process.

Once the aesthetic coating suspension is consumed, the tablets are dried in the coating pan for about 5 minutes with a pan speed of about 2-8 rpms and an exhaust temperature of 25 ± 5°C. Once the tablets are dried, the exhaust air is turned off and the pan speed is adjusted to about 3-4 rpms and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen is sprinkled onto the tablets. After the tablets have rolled in the wax for about 5 minutes the exhaust air is turned on and the tablets are rolled for an additional 10 minutes.

The finished polished tablet exhibited the following pioglitazone HCl dissolution profile when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution:

Time	**% Pioglitazone Released**
10 min.	42%
20 min	79%
30 min	95%
45 min	102%

The finished polished tablet also contained the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5µm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40µL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

Name	Relative Retention Time	Amount (%)
RS-1	0.7	N.D*.
Pioglitazone	1.0	
RS-2	1.5	0.03

RS-3	3.4	0.04
RS-4	1.2	0.03
RS-5	2.8	0.04

*N.D. = none detected

RS-1 is (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-5-hydroxy-2,4-thiazolidinedione.

RS-2 is (z)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidene]-2,4-thiazolidinedione.

RS-3 is (+/-)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-3-[2-(5-ethyl-2-pyridyl)ethyl]-2,4-thiazolidinedione.

RS-4 is (+/-)-ethyl-2-carbamoyltio-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl-]propionate.

RS-5 is ethyl-3-p-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl-propionate.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 2g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for three (3) months. After storage, the final polished tablet was tested and exhibited the following pioglitazone HCl dissolution profile when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution:

Time	% Pioglitazone Released
10 min.	38%
20 min	73%
30 min	92%
45 min	101%

The stored final polished tablet also contained the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5µm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40µL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

Name	Relative Retention Time	Amount (%)
RS-1	0.7	N.D.*
Pioglitazone	1.0	

RS-2	1.5	0.03
RS-3	3.4	0.03
RS-4	1.2	0.02
RS-5	2.8	0.04

*N.D. = none detected

EXAMPLE 7

A controlled release tablet containing 1000 mg of metformin HCl and 30 mg pioglitazone was prepared as follows:

A. First Active Drug Core

A cellulose acetate coated metformin HCL tablet is prepared as described in Example 5.

B. Second Active Drug

An immediate release amount of pioglitazone HCL was applied to the 1000 mg metformin HCl membrane coated tablets prepared above in step A. The final tablet had the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	9.0 mg/tablet
Lactose Monohydrate, NF (modified spray dried)	30.0 mg/tablet
Polyethylene Glycol 8000, NF	0.450 mg/tablet
Titanium Dioxide, USP	0.90 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

The seal coat was applied to approximately 12.09 kg of the 1000 mg metformin HCl membrane coated tablet prepared in step A described above. The seal coating was prepared by dispersing about 0.91 kg of Opadry Clear (YS-1-7006) in about 1.133 kg of purified water for 30 minutes. The dispersion was sprayed onto approximately 12.09 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C ± 5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The pioglitazone coating was applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating was prepared by slowly dispersing about 0.104 kg of hydroxypropyl cellulose, NF (HPC-SLL) in about 8.499 kg of purified water. The HPC-SSL and water was mixed for about 20 minutes, then 0.347 kg of lactose monohydrate, NF (modified spray dried) was added to the HPC-SSL/water mixture and mixed for about 2 minutes. After the lactose was mixed in, approximately 0.005 kg of polyethylene glycol 8000 NF and 0.010 kg of titanium dioxide, USP were added to the water, HPC-SSL and lactose mixture and mixed for about 5 minutes. After about 5 minutes of mixing about 0.383 kg pioglitazone hydrochloride was dispersed into the coating solution. This coating solution contained approximately 15% excess material to compensate for material loss during the coating process. The pioglitazone suspension was stirred until the suspension was consumed during the coating process. The pioglitazone HCl suspension was applied to the seal coated 1000 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed, 3 spray guns with the following conditions:

Spray Rate	20±10 mL/gun/min
Exhaust Temperature	40±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms

Pattern Air Pressure	10-40 psi
Supply Air Flow	300±100 CFM

Once the pioglitazone tablets were dried, the exhaust air was turned off and the pan speed was adjusted to about 3-4 rpms and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen was sprinkled onto the tablets. After the tablets have rolled in the wax for about 5 minutes the exhaust air was turned on and the tablets were rolled for an additional 10 minutes.

The finished polished tablet released greater than 95% of the pioglitazone when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution. The final tablets also exhibited a hardness greater than 35 kp and a friability of 0.00%. The final tablet was tested for pioglitazone related compounds by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector. The results of the test are reported in Table 1 below.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 3g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for fifteen days, 1 month 2 months, 3 months and 6 months. After storage, the final polished tablet was tested and found to contain the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

TABLE 1

Name	Initial (%)	0.5 M (%)	1M (%)	2 M (%)	3M (%)	6M (%)
RS-1	0.01	0.01	0.01	N.D.	N.D.	N.D.
RS-2	0.02	0.03	0.03	0.02	0.03	0.02
RS-3	0.03	0.04	0.03	0.03	0.04	0.04
RS-4	0.03	0.02	0.03	0.03	0.02	0.02

RS-5	0.04	0.04	0.04	0.04	0.03	0.04

"M" = months

EXAMPLE 8

A controlled release tablet containing 1000 mg of metformin HCl and 30 mg pioglitazone was prepared as follows:

A. First Active Drug Core

A cellulose acetate coated metformin HCl tablet core was prepared according to the procedure described in Example 5.

B. Second Active Drug

An immediate release amount of pioglitazone HCL was applied to the 1000 mg metformin HCl membrane coated tablets prepared above in step A. The final tablet had the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	33.06 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	9.0 mg/tablet
Lactose Monohydrate, NF (modified spray dried)	30.0 mg/tablet
Polyethylene Glycol 8000, NF	0.450 mg/tablet
Titanium Dioxide, USP	0.90 mg/tablet
Color Coating	
Hydroxypropyl Cellulose, NF (HPC-SSL)	5.5 mg/tablet
Polyethylene Glycol 8000, NF	1.38 mg/tablet
Titanium Dioxide, USP	0.60 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

The seal coat was applied to approximately 13.02 kg of the 1000 mg metformin HCl membrane coated tablet prepared in step A described above. The seal coating was prepared by dispersing about 0.098 kg of Opadry Clear (YS-1-7006) in about 1.220 kg of purified water for 30 minutes. The dispersion was then sprayed onto approximately 13.02 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C ± 5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The pioglitazone coating then was applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating was prepared by slowly dispersing about 0.108 kg of hydroxypropyl cellulose (HPC-SLL) in about 8.753 kg of purified water. The HPC-SSL and water was mixed for about 20 minutes, after which 0.358 kg of lactose monohydrate, NF (modified spray dried) was added to the HPC-SSL/water mixture and mixed for about 2 minutes. After the lactose was mixed in, approximately 0.006 kg of polyethylene glycol 8000 NF and 0.011 kg of titanium dioxide, USP were added to the water, HPC-SSL and lactose mixture and mixed for about 5 minutes. After about 5 minutes of mixing about 0.394 kg pioglitazone hydrochloride was dispersed into the coating solution. This coating solution contained approximately 10% excess material to compensate for material loss during the coating process. The pioglitazone suspension was stirred until the suspension was consumed during the coating process. The pioglitazone HCl suspension was applied to the seal coated 1000 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed, 3 spray guns, with the following conditions:

Spray Rate	20±10 mL/gun/min
Exhaust Temperature	40±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms

Pattern Air Pressure	10-40 psi
Supply Air Flow	300±100 CFM

Once the pioglitazone coating was applied to the seal coated 1000 mg metformin HCl membrane coated tablets, a color or aesthetic coating was applied to the pioglitazone coated tablet. The color coating was prepared by dispersing about 0.060 kg of HPC-SSL, NF 0.015 kg of polyethylene glycol 8000, NF and 0.007 titanium dioxide, USP in 0.810 kg of purified water and mixing the dispersion for about 30 minutes. The color coating was than sprayed onto the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The color coating dispersion was continuously stirred until the dispersion was consumed during the coating process.

Once the color coating suspension was consumed, the tablets were dried in the coating pan for about 5 minutes with a pan speed of about 2-8 rpms and an exhaust temperature of 40 ± 5°C. Once the tablets were dried, the exhaust air is turned off and the pan speed is adjusted to about 3-4 rpms and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen was sprinkled onto the tablets. After the tablets were rolled in the wax for about 5 minutes the exhaust air was turned on and the tablets were rolled for an additional 10 minutes.

The finished polished tablet released greater than 90% of the pioglitazone when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution. The average of the 12 vessel tested was 96% released. The final tablets also exhibited a hardness greater than 35 kp and a friability of 0.1%. The final tablet was tested for pioglitazone related compounds by HPLC using a YMC-ODS-AQ, 5µm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40µL injection volume, 0.7 mL/min flow rate,

25°C column temperature and 269 nm wavelength for the UV dectector. The results of the test are reported in Table 2 below.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 3g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for fifteen days, 1 month, 2 months, 3 months and 6 months. After storage, the final polished tablet was tested and found to contain the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5µm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40µL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

TABLE 2

Name	Initial (%)	0.5 M (%)	1M (%)	2 M (%)	3M (%)	6M (%)
RS-1	0.01	0.01	0.01	N.D.	N.D.	N.D.
RS-2	0.02	0.03	0.03	0.02	0.03	0.03
RS-3	0.03	0.03	0.03	0.03	0.04	0.04
RS-4	0.02	0.02	0.03	0.02	0.02	0.01
RS-5	0.04	0.04	0.03	0.04	0.04	0.04

EXAMPLE 9

A controlled release tablet containing 1000 mg of metformin HCl and 15 mg pioglitazone is prepared as follows:

I. First Active Drug

A 1000 mg membrane coated tablet is prepared as described in Example 5 above. The 1000 mg membrane coated tablet has the following composition:

CORE

Metformin HCl	1000 mg/tablet
Povidone K-90, USP	78.0 mg/tablet
Sodium Lauryl Sulfate, NF	51.69 mg/tablet

Magnesium Stearate, NF	5.65 mg/tablet
SEAL COATING	
Opadry Clear (YS-1-7006)	47.05 mg/tablet
MEMBRANE COATING	
Cellulose Acetate, 398-10, NF	15.77 mg/tablet
Triacetin, USP	0.92 mg/tablet
Polyethylene Glycol 400, NF	1.85 mg/tablet
Total weight	1201.0 mg/tablet

II. Second Active Drug

An immediate release amount of pioglitazone HCl was applied to the 1000 mg metformin HCl membrane coated tablets prepared in step I. The final tablet had the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	21.0 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	16.53 mg/tablet
Sodium Chloride	2.5 mg/tablet
Opadry Clear (YS-1-7006)	1.850 mg/tablet
Color Coating	
Opadry II White (Y-22-7719)	21.54 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

The seal coat was applied to the 1000 mg metformin HCl membrane coated tablet. The seal coating was prepared by dispersing 0.249 kg of Opadry Clear in 4.981 kg of alcohol USP and mixing the dispersion for 15 minutes. The dispersion was then sprayed onto approximately 14.24 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25°C ± 5°C
Atomization Air Pressure	10-40 psi

Pan Speed	4-9 rpm
Supply Air Flow	300±150 CFM
Pattern Air Pressure	10-40 psi

The seal coating dispersion was continuously stirred until it was consumed during the coating process.

The pioglitazone coating was applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating was prepared by mixing 3.793 kg of alcohol USP and 1.07 kg of purified water and slowly dispersing 0.024 kg of Opadry Clear into the solvent mixture. Once the Opadry Clear was dispersed, it was homogenized for about 10 minutes. Once the Opadry Clear dispersion was homogenized, 0.032 kg of sodium chloride was added to the dispersion and homogenized for about 2 minutes. After the sodium chloride was homogenized, 0.212 kg of pioglitazone HCl was slowly dispersed into the solvent mix and then homogenized for about 10 minutes. Once the pioglitazone HCl was homogenized, the homogenizer was removed from the mixing vessel and replaced with an air mixer and mixed for an additional 15 minutes. The pioglitazone suspension was stirred until the suspension was consumed during the coating process. This coating solution contained approximately 8% excess material to compensate for material loss during the coating process. The pioglitazone HCl suspension was applied to the seal coated 1000 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	25±10 mL/gun/min
Exhaust Temperature	25±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms
Pattern Air Pressure	10-40 psi
Supply Air Flow	300±150 CFM

Once the pioglitazone coating was applied to the seal coated 1000 mg metformin HCl membrane coated tablets, a color or aesthetic coating of Opadry II White was applied to the pioglitazone coated tablet. The aesthetic coating was prepared by dispersing 0.255 kg of Opadry II White (Y-22-7719) in 5.109 kg of

alcohol USP and mixing the dispersion for about 1 hour. The Opadry II White dispersion was sprayed onto the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25°C±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±150 CFM
Pattern Air Pressure	10-40 psi

The color coating dispersion was continuously stirred until the dispersion was consumed during the coating process.

Once the aesthetic coating suspension was consumed, the tablets was dried in the coating pan for about 5 minutes with a pan speed of about 2-8 rpms and an exhaust temperature of 25 ± 5°C. Once the tablets were dried, the exhaust air was turned off and the pan speed was adjusted to about 3-4 rpms and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen was sprinkled onto the tablets. After the tablets have rolled in the wax for about 5 minutes the exhaust air was turned on and the tablets are rolled for an additional 10 minutes.

The finished polished tablet released an average of 95% of the pioglitazone when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution The final tablets also exhibited a hardness greater than 35 kp and a friability of 0.00%. The final tablet was tested for pioglitazone related compounds by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector. The results of the test are reported in Table 3 below.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 2g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for one month. After storage, the final polished tablet was tested and found to contain the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1)

mobile phase, a 40µL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

TABLE 3

Name	Relative Retention Time	Initial Amount (%)	1 month Amount(%)
RS-1	0.7	ND	ND
Pioglitazone	1.0		
RS-2	1.5	0.02	0.02
RS-3	3.4	0.03	0.05
RS-4	1.2	0.03	0.02
RS-5	2.8	0.05	0.04

EXAMPLE 10

A controlled release tablet containing 1000 mg of metformin HCl and 15 mg pioglitazone was prepared as follows:

A. First Active Drug Core

A cellulose acetate coated metformin HCL tablet is prepared as described in Example 5.

B. Second Active Drug

An immediate release amount of pioglitazone HCL was applied to the 1000 mg metformin HCl membrane coated tablets prepared above in step A. The final tablet has the following composition:

Metformin HCl membrane coated tablet	1201.0 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	9.00 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	16.53 mg/tablet
Hydroxypropyl Cellulose, NF (HPC-SSL)	4.5 mg/tablet

Lactose Monohydrate, NF (modified spray dried)	15.0 mg/tablet
Polyethylene Glycol 8000, NF	0.225 mg/tablet
Titanium Dioxide, USP	0.450 mg/tablet
Color Coating	
Hydroxypropyl Cellulose, NF (HPC-SSL)	5.5 mg/tablet
Polyethylene Glycol 8000, NF	1.375 mg/tablet
Titanium Dioxide, USP	0.60 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.40 mg/tablet

The seal coat was applied to approximately 14.36 kg of the 1000 mg metformin HCl membrane coated tablet prepared in step A described above. The seal coating was prepared by dispersing about 0.108 kg of Opadry Clear (YS-1-7006) in about 1.345 kg of purified water for 30 minutes. The dispersion was then sprayed onto approximately 14.36 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C ± 5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The pioglitazone coating was applied to the seal coated 1000 mg metformin HCl membrane coated tablets. The pioglitazone coating was prepared by slowly dispersing about 0.059 kg of hydroxypropyl cellulose (HPC-SLL) in about 6.034 kg of purified water. The HPC-SSL and water was mixed for about 20 minutes, then 0.197 kg of lactose monohydrate, NF (modified spray dried) was added to the HPC-SSL/water mixture and mixed for about 2 minutes. After the lactose was mixed in, approximately 0.003 kg of polyethylene glycol 8000 NF and 0.006 kg of titanium dioxide, USP were added to the water, HPC-SSL, NF and lactose mixture and mixed for about 5 minutes. After about 5 minutes of mixing about 0.217 kg pioglitazone

hydrochloride was dispersed into the coating solution. This coating solution contained approximately 10% excess material to compensate for material loss during the coating process. The pioglitazone suspension was stirred until the suspension was consumed during the coating process. The pioglitazone HCl suspension was applied to the seal coated 1000 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed, 3 spray guns, with the following conditions:

Spray Rate	20±10 mL/gun/min
Exhaust Temperature	40±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms
Pattern Air Pressure	10-40 psi
Supply Air Flow	300±100 CFM

Once the pioglitazone coating was applied to the seal coated 1000 mg metformin HCl membrane coated tablets, a color or aesthetic coating was applied to the pioglitazone coated tablet. The color coating was prepared by dispersing about 0.066 kg of HPC-SSL, 0.016 kg of polyethylene glycol 8000, NF and 0.007 titanium dioxide, USP in 0.894 kg of purified water and mixing the dispersion for about 30 minutes. The color coating was sprayed onto the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The color coating dispersion was continuously stirred until the dispersion was consumed during the coating process.

Once the color coating suspension was consumed, the tablets were dried in the coating pan for about 5 minutes with a pan speed of about 2-8 rpms and an exhaust temperature of 40 ± 5°C. Once the tablets were dried, the exhaust air was turned off

and the pan speed was adjusted to about 3-4 rpms and 0.005 kg of Candellia wax powder that had been passed through a 60 mesh screen was sprinkled onto the tablets. After the tablets were rolled in the wax for about 5 minutes the exhaust air was turned on and the tablets were rolled for an additional 10 minutes.

The finished polished tablet released greater than 95% of the pioglitazone when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution. The final tablets also exhibited a hardness greater than 35 kp and a friability of 0.0%. The final tablet was tested for pioglitazone related compounds by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector. The results of the test are reported in Table 4 below.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 3g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for fifteen days, 1 month, 2 months and 3 months. After storage, the final polished tablet was tested and found to contain the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

TABLE 4

Name	Initial (%)	0.5 M (%)	1M (%)	2 M (%)	3M (%)
RS-1	N.D.	0.01	N.D.	N.D.	N.D.
RS-2	0.02	0.03	0.03	0.03	0.02
RS-3	0.03	0.04	0.04	0.04	0.03
RS-4	0.03	0.02	0.02	0.02	0.02
RS-5	0.03	0.04	0.05	0.04	0.04

EXAMPLE 11

A controlled release tablet containing 500 mg of metformin HCl and 15 mg pioglitazone was prepared as follows:

A. First Active Drug Core

I. Metformin Granules	(% composition)
Metformin HCl	92.76%
Povidone K-90, USP	7.24%

About 139.14 kg of metformin HCl was delumped by passing it through a comil equipped with a number 813 screen and no spacer at 840-850 rpm and collecting it in a clean, polyethylene-lined container. About 10.86 kg of povidone, K-30 was dissolved in about 206.34 kg of purified water. The delumped metformin HCl was then added to a top-spray fluidized bed granulator (Glatt Brand GPCG-60) and granulated by spraying the binding solution of povidone and water under the following conditions: product temperature of about 38-43°C, inlet air temperature of 60-95°C; atomization air pressure of 2.5-3 bars and spray rate of 500 g/min (491-515 g/min) for first 15 minutes, 700 g/min (680-710 g/min) for 15-30 minutes, 900 g/min (860-910 g/min) for 30-45 minutes, 1100 g/min (1090-1170 g/min) for 45-60 minutes and about 1200 g/min (1170-1220 g/min) for the remainder of the spray time. After the binding solution has been sprayed, the granules were dried in the fluidized bed until the loss on drying (LOD) was less than 2%.

Once the granules were dried, they are passed through a Comil equipped with a number 1143 stainless steel screen and a #075 spacer at a speed of 1086-1088 rpms. The above process was repeated a second time to produce a total of about 300 kg of metformin granules.

II. Metformin Blend	(% composition)
Metformin HCl Granules	94.95%
Sodium Lauryl Sulfate, NF	4.55%
Magnesium Stearate, NF	0.50%

The about 300 kg of metformin granules prepared above in step I were added to a 50 cu. ft. slant cone blender along with about 14.38 kg of sodium lauryl sulfate,

NF and blended for about 20 minutes. About 1.58 kg of magnesium stearate, NF was then passed through a 40 mesh stainless steel sieve and added to the slant cone blender and blended for an additional five minutes.

The blend was compressed into metformin uncoated cores using a rotary press fitted with 15/32" round compound cup, pre-compression force of 14 kp and main compression force of 34 kp. The resulting tablets has a weight between 523-613 g with a target weight of 568 g, hardness between 14-26 kp (target of 20 kp) and a friability of less than or equal to 0.8%.

III. Metformin Seal Coated Tablets	(% composition)
Metformin HCl Uncoated Tablets	96.02%
OPADRY Clear (YS-1-7006)	3.98%

Approximately 57.61 kg of the uncoated tablets prepared in step II above were seal coated by applying a solution of about 2.388 kg of OPADRY Clear (YS-1-7006) and 21.50 kg of purified water onto the tablets using a pan coater. The pan coater was a 36 inch O'Hara Labcoat III with three (3) spray guns at a distance of 8-11 inches from the bed. The coating conditions were:

Exhaust Temperature:	40-47°C
Atomization Pressure	50±10 psi
Air Volume	1000±200 CFM
Spray Rate	180±60 g/min (60±20ml/gun/min)
Pan Speed	4-8 rpm.

IV Membrane	(% composition)
Metformin Seal Coated Tablets	95.521%
Cellulose Acetate (398-10)[2]	3.807%
Triacetin	0.145%
PEG 400	0.289%

[2] acetyl content 39.3-40.3%

(a) Membrane Coating Process

Approximately 51.06 kg of acetone is added to a stainless steel tank followed by about 2.281 kg of cellulose acetate and mixed for about 20 minutes until the solution becomes clear. Once the solution is clear about 0.269 kg of polyethylene glycol 400 is added to the solution and mixed for about 5 minutes followed by the addition of about 0.135 kg of triacetin. The solution is mixed for an additional 5 minutes.

About 59.07 kg of the seal coated metformin HCl tablets are loaded into a GPCG-60 (Glatt) brand fluidized bed coater with Wurster insert (size 18" by 45 mm high) with a nozzle of size 1.5 mm. The seal coated metformin HCl tablets areis fluidized and the product temperature is adjusted to about 21±3°C. The cellulose acetate solution is sprayed onto the fluidized seal coated metformin HCl tablets with an atomization pressure of about 2.0-3.0 bars, air volume of 1400 ± 300 CFM and a spray rate of 400±100 g/min until a weight gain of 3-5% (target 3.8%) is obtained. Once the desired amount of membrane coating has been applied the membrane coated tablets are dried in the fluidized bed 21±3°C and 1200±100 CFM for about 10 minutes followed by 40°C and 1200±100 CFM for about 5 minutes.

The resulting membrane coated tablets are laser drilled to create an orifice in the approximate center of each side of the membrane coated tablet (i.e 2 orifices) with an average diameter of 0.5 mm per orifice. The top micrometer is 5.4 ± 2 mm, bottom micrometer is 6.75 ±2 mm, the pulse width of the laser is 170±70 and pulse delay of 290 ±150.

B. Second Active Drug

An immediate release amount of pioglitazone HCL was applied to the 500 mg metformin HCl membrane coated tablets prepared in step A. The final tablet had the following composition:

Metformin HCl membrane coated tablet	618.9 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	11.5 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	16.53 mg/tablet
Sodium Chloride	2.5 mg/tablet
Opadry Clear (YS-1-7006)	1.850 mg/tablet
Color Coating	

Opadry II White (Y-22-7719)	10.77 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.20 mg/tablet

The seal coat was applied to the 500 mg metformin HCl membrane coated tablet. The seal coating was prepared by dispersing 0.243 kg of Opadry Clear in 3.473 kg of alcohol USP and mixing the dispersion for 15 minutes. The dispersion was then sprayed onto approximately 13.08 kg of the 1000 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25°C ± 5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	200±100 CFM
Pattern Air Pressure	10-40 psi

The seal coating dispersion was continuously stirred until it was consumed during the coating process.

The pioglitazone coating then was applied to the seal coated 500 mg metformin HCl membrane coated tablets. The pioglitazone coating was prepared by mixing 5.656 kg of alcohol USP and 1.595 kg of purified water and slowly dispersing 0.045 kg of Opadry Clear into the solvent mixture. Once the Opadry Clear was dispersed, it was homogenized for about 10 minutes. Once the Opadry Clear dispersion was homogenized, 0.061 kg of sodium chloride was added to the dispersion and homogenized for about 2 minutes. After the sodium chloride is homogenized, 0.402 kg of pioglitazone HCl was slowly dispersed into the solvent mix and then homogenized for about 10 minutes. Once the pioglitazone HCl was homogenized, the homogenizer was removed from the mixing vessel and replaced with an air mixer and mixed for an additional 15 minutes. The pioglitazone suspension was stirred until the suspension is consumed during the coating process. This coating solution contained approximately 15% excess material to compensate for material loss during the coating process. The pioglitazone HCl suspension was applied to the seal coated 500 mg metformin HCl membrane coated tablet cores using

a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed with 3 spray guns and the following conditions:

Spray Rate	25±10 mL/gun/min
Exhaust Temperature	25±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms
Pattern Air Pressure	10-40 psi
Supply Air Flow	200±100 CFM

Once the pioglitazone coating was applied to the seal coated 500 mg metformin HCl membrane coated tablets, a color or aesthetic coating of Opadry II White was applied to the pioglitazone coated tablet. The aesthetic coating was prepared by dispersing 0.228 kg of Opadry II White (Y-22-7719) in 3.253 kg of alcohol USP and mixing the dispersion for about 1 hour. The Opadry II White dispersion was than sprayed onto the pioglitazone HCl coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	25 ± 10 mL/gun/min
Exhaust Temperature	25°C±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	200±100 CFM
Pattern Air Pressure	10-40 psi

The color coating dispersion was continuously stirred until the dispersion was consumed during the coating process.

Once the aesthetic coating suspension was consumed, the tablets were dried in the coating pan for about 5 minutes with a pan speed of about 2-8 rpms and an exhaust temperature of 25 ± 5°C. Once the tablets were dried, the exhaust air was turned off and the pan speed was adjusted to about 3-4 rpms and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen was sprinkled onto the tablets. After the tablets rolled in the wax for about 5 minutes the exhaust air was turned on and the tablets were rolled for an additional 10 minutes.

The finished polished tablet released greater than of 95% of the pioglitazone when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution The final tablets also exhibited a hardness greater than 35 kp and a friability of 0.00%. The final tablet was tested for pioglitazone related compounds by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector. The results of the test are reported in Table 5 below.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 1g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for one month. After storage, the final polished tablet was tested and found to contain the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

TABLE 5

Name	Initial (%)	1 M (%)
RS-1	N.D.	N.D.
RS-2	0.03	0.03
RS-3	0.04	0.05
RS-4	0.03	0.02
RS-5	0.04	0.04

EXAMPLE 12

A controlled release tablet containing 500 mg of metformin HCl and 15 mg pioglitazone was prepared as follows:

A. First Active Drug Core

The 500 mg cellulose acetate metformin HCl core was prepared as described in Example 11.

B. Second Active Drug

An immediate release amount of pioglitazone HCL was applied to the 500 mg metformin HCl membrane coated tablets prepared above in step A. The final tablet had the following composition:

Metformin HCl membrane coated tablet	618.9 mg/tablet
Seal Coat	
Opadry Clear (YS-1-7006)	4.50 mg/tablet
Pioglitazone Coating	
Pioglitazone HCl	16.53 mg/tablet
Hydroxypropyl Cellulose (HPC-SSL)	6.0 mg/tablet
Lactose Monohydrate, NF (modified spray dried)	50.0 mg/tablet
Polyethylene Glycol 8000, NF	0.300 mg/tablet
Titanium Dioxide, USP	0.600 mg/tablet
Color Coating	
Hydroxypropyl Cellulose (HPC-SSL)	2.75 mg/tablet
Polyethylene Glycol 8000, NF	0.688 mg/tablet
Titanium Dioxide, USP	0.300 mg/tablet
Polishing Coat	
Candelilla Wax Powder	0.20 mg/tablet

The seal coat was applied to approximately 12.36 kg of the 500 mg metformin HCl membrane coated tablet prepared in step A described above. The seal coating was prepared by dispersing about 0.090 kg of Opadry Clear (YS-1-7006) in about 1.124 kg of purified water for 30 minutes. The dispersion was then sprayed onto approximately 12.36 kg of the 500 mg metformin HCl tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C ± 5°C
Atomization Air Pressure	10-40 psi

Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The pioglitazone coating then was applied to the seal coated 500 mg metformin HCl membrane coated tablets. The pioglitazone coating was prepared by slowly dispersing about 0.134 kg of hydroxypropyl cellulose (HPC-SLL) in about 13.692 kg of purified water. The HPC-SSL and water was mixed for about 20 minutes, then 1.119 kg of lactose monohydrate, NF (modified spray dried) was added to the HPC-SSL/water mixture and mixed for about 2 minutes. After the lactose was mixed in, approximately 0.007 kg of polyethylene glycol 8000 NF and 0.013 kg of titanium dioxide, USP were added to the water, HPC-SSL and lactose mixture and mixed for about 5 minutes. After about 5 minutes of mixing about 0.370 kg pioglitazone hydrochloride was dispersed into the coating solution. This coating solution contained approximately 12% excess material to compensate for material loss during the coating process. The pioglitazone suspension was stirred until the suspension is consumed during the coating process. The pioglitazone HCl suspension was applied to the seal coated 500 mg metformin HCl membrane coated tablet cores using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4 ±2" above the top of the static bed, 3 spray guns, with the following conditions:

Spray Rate	20±10 mL/gun/min
Exhaust Temperature	40±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpms
Pattern Air Pressure	10-40 psi
Supply Air Flow	300±100 CFM

Once the pioglitazone coating was applied to the seal coated 500 mg metformin HCl membrane coated tablets, a color or aesthetic coating was applied to the pioglitazone coated tablet. The color coating was prepared by dispersing about 0.055 kg of HPC-SSL, NF 0.014 kg of polyethylene glycol 8000, NF and 0.006 titanium dioxide, USP in 0.747 kg of purified water and mixing the dispersion for about 30 minutes. The color coating was than sprayed onto the pioglitazone HCl

coated tablets using a 24" O'Hara Labcoat III pan coater with the nozzle tip set 4±2" from the top of the static bed, 3 spray guns and the following conditions:

Spray Rate	20 ± 10 mL/gun/min
Exhaust Temperature	40°C±5°C
Atomization Air Pressure	10-40 psi
Pan Speed	4-9 rpm
Supply Air Flow	300±100 CFM
Pattern Air Pressure	10-40 psi

The color coating dispersion was continuously stirred until the dispersion was consumed during the coating process.

Once the color coating suspension was consumed, the tablets were dried in the coating pan for about 5 minutes with a pan speed of about 2-8 rpms and an exhaust temperature of 40 ± 5°C. Once the tablets were dried, the exhaust air was turned off and the pan speed was adjusted to about 3-4 rpms and 0.004 kg of Candellia wax powder that had been passed through a 60 mesh screen was sprinkled onto the tablets. After the tablets rolled in the wax for about 5 minutes the exhaust air was turned on and the tablets were rolled for an additional 10 minutes.

The finished polished tablet released greater than 95% of the pioglitazone when tested in a USP apparatus type 1 at 100 rpm in a pH 2.0 HCl-0.3M KCl buffer solution. The final tablets also exhibited a hardness greater than 35 kp and a friability of 0.01%. The final tablet was tested for pioglitazone related compounds by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector. The results of the test are reported in Table 6 below.

The final polished tablet was packaged in a 100 cc HDPE bottle containing one (1) 3g SORB-IT® desiccant canister and subjected to accelerated stability conditions of 40°C and 75% relative humidity for 1 month and 2 months. After storage, the final polished tablet was tested and found to contain the following pioglitazone related compounds when tested by HPLC using a YMC-ODS-AQ, 5μm, 120Å, 4.6 x 250 mm column, a 0.1 M ammonium acetate buffer:acetonitrile:glacial acetic acid (25:25:1) mobile phase, a 40μL injection volume, 0.7 mL/min flow rate, 25°C column temperature and 269 nm wavelength for the UV dectector.

TABLE 6

Name	Initial (%)	1M (%)	2M (%)
RS-1	N.D.	N.D.	N.D.
RS-2	0.02	0.02	0.02
RS-3	0.03	0.03	0.04
RS-4	0.03	0.02	0.02
RS-5	0.04	0.03	0.04

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

What is claimed is:

1. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising:

(a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and

(b) an immediate release thiazolidinedione derivative containing component that comprises a thiazolidinedone derivative and a low viscosity water soluble binder;

wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

2. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

3. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

4. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 45 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

5. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

6. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 40

minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

7. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

8. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 40 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

9. The pharmaceutical dosage form as defined in claim 1 wherein not less than 85%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

10. The pharmaceutical dosage form as defined in claim 1 wherein not less than 90%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

11. The pharmaceutical dosage form as defined in claim 1 wherein not less than 95%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

12. The pharmaceutical dosage form as defined in claim 1 wherein not less than 100%, of the thiazolidinedione is released from the dosage form within 30 minutes when tested according to the United States Pharmacopeia (USP) 26, with Apparatus 1 at 100 rpm, 37 °C and 900 ml of 0.3 M KCl-HCl Buffer, pH 2.0.

13. A pharmaceutical dosage form having a first and second active drug, said dosage form comprising:

(a) a controlled release core comprising an antihyperglycemic drug and at least one pharmaceutically acceptable excipient; and

(b) an immediate release thiazolidinedione derivative containing component that comprises a thiazolidinedone derivative and a low viscosity water soluble binder; wherein the total thiazolidinedione related compounds or impurities in the final dosage form are not more than 0.6 as determined by high performance liquid chromatography.

14. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%.

15. The pharmaceutical dosage form as defined in claim 13 wherein the total thiazolidinedione related compounds are not more than 0.5%.

16. The pharmaceutical dosage form as defined in claim 13 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.25%.

17. The pharmaceutical dosage form as defined in claim 16 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.20%.

18. The pharmaceutical dosage form as defined in claim 17 wherein each individual thiazolidinedione related compound or impurity in the final dosage form is not more than 0.10%.

19. The dosage form of claim 1 wherein said controlled release core is an osmotic tablet.

20. The dosage form of claim 19 wherein the osmotic tablet comprises:

(a) a core comprising:

(i) 50-98% of said antihyperglycemic drug;

(ii) 0.1-40% of a binding agent;

(iii) 0-20% of an absorption enhancer; and

(iv) 0-5% of a lubricant;

(b) optionally a seal coat surrounding the core; and

(c) a sustained release membrane comprising:

(i) 50-99% of a polymer;

(ii) 0-40% of a flux enhancer and

(iii) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.

21. The dosage form of claim 1 wherein said antihyperglycemic drug is a biguanide.

22. The dosage form of claim 1 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.

23. The dosage form of claim 1 wherein said core is substantially free from any gelling or expanding polymer.

24. The dosage form of claim 1 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 6-12 hours.

25. The dosage form of claim 1 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.

26. The dosage form of claim 25 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.

27. The dosage form of claim 13 wherein said controlled release core is an osmotic tablet.

28. The dosage form of claim 27 wherein the osmotic tablet comprises:

(d) a core comprising;

(i) 50-98% of said antihyperglycemic drug;

(ii) 0.1-40% of a binding agent;

(iii) 0-20% of an absorption enhancer; and

(iv) 0-5% of a lubricant;

(e) optionally a seal coat surrounding the core; and

(f) a sustained release membrane comprising;

(iv) 50-99% of a polymer;

(v) 0-40% of a flux enchancer and

(vi) 0-25% of a plasticizer, said membrane having at least one passageway formed therein for release of the antihyperglycemic drug.

29. The dosage form of claim 13 wherein said antihyperglycemic drug is a biguanide.

30. The dosage form of claim 13 wherein said thiazolidinedione derivative is troglitazone, rosiglitazone, pioglitazone, ciglitazone or pharmaceutically acceptable salts, isomers or derivatives thereof.

31. The dosage form of claim 13 wherein said core is substantially free from any gelling or expanding polymer.

32. The dosage form of claim 13 wherein said controlled release of said antihyperglycemic drug provides a Tmax of 6-12 hours.

33. The dosage form of claim 13 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-12 hours.

34. The dosage form of claim 33 wherein said release of the thiazolidinedione derivative provides a Tmax of 1-4 hours.

35. The dosage form of claim 1 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 50 mPa.S when tested as a 2% aqueous solution at 20°C.

36. The dosage form of claim 35 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 25 mPa.S when tested as a 2% aqueous solution at 20°C.

37. The dosage form of claim 35 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 10 mPa.S when tested as a 2% aqueous solution at 20°C.

38. The dosage form of claim 35 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity between 2 and 6 mPa.S when tested as a 2% aqueous solution at 20°C.

39. The dosage form of claim 37 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.

40. The dosage form of claim 38 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.

41. The dosage form of claim 13 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 50 mPa.S when tested as a 2% aqueous solution at 20°C.

42. The dosage form of claim 41 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 25 mPa.S when tested as a 2% aqueous solution at 20°C.

43. The dosage form of claim 41 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity of less than 10 mPa.S when tested as a 2% aqueous solution at 20°C.

44. The dosage form of claim 41 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component has a viscosity between 2 and 6 mPa.S when tested as a 2% aqueous solution at 20°C.

45. The dosage form of claim 43 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.

46. The dosage form of claim 44 wherein the water soluble binder of the immediate release thiazolidinedione derivative containing component is hydroxypropyl cellulose.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/09082

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61K 9/00(2006.01)

USPC: 424/400
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,099,862 A (CHEN et al.) 08 August 2000 (08.08.2000), abstract, col. 2, lines 40-55, col. 3, lines 5-65 and cols. 5-7, examples 1-2.	1-46
Y	US 4,687,777 A (MEGURO et al.) 18 August 1987 (18.08.1987), col. 1, lines 5-15, col. 2, lines 15-65 and cols. 6-7, example 1.	1-46

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search
08 July 2006 (08.07.2006)

Date of mailing of the international search report
20 JUL 2006

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Form PCT/ISA/210 (second sheet) (April 2005)